REMARKS

Rejections under 35 U.S.C. §112, 2nd paragraph

Claims 1 and 19 have been rejected under 35 U.S.C. §112, 2nd paragraph for being unclear in the recitation of "corresponding to." Claim 1 has been amended to replace "corresponding to" with the more typically used "comprising." Applicants note that claim 19 does not recite "corresponding to." Withdrawal of the rejection is therefore respectfully requested.

Rejection under 35 U.S.C. §112, 1st paragraph

The Examiner maintains the rejection of claim 1 under 35 U.S.C. §112, 1st paragraph, as lacking adequate written description for any sequences other than SEQ ID NOS:1 and 2. Applicants traverse this rejection and withdrawal thereof is respectfully requested. The high-affinity binding site itself of the interferons is a previously characterized and well-known conserved sequence. See for example, Zav'yalov V.P. et al. FEBS Lett. Vol. 278, 187-189 (1991) and Zav'yalov V.P. et al. Mol. Immunol. Vol. 32, 425-431 (1995), both of which were published prior to the present invention. It is the anti-proliferative activity associated with this site that is described for the first time by the present inventors. Thus, the present situation is completely

different from the *University of California v. Eli Lilly* case and the other cited court cases because the portion of the interferon proteins that contributes to the observed activity is already known. As such, the invention as claimed is fully supported by the written description in the specification and withdrawal of the rejection is respectfully requested.

Rejections under 35 U.S.C. §103

The Examiner maintains the following rejections under 35 U.S.C. §103: claim 1 as being obvious over Charak et al. combined with Cruse et al.; claims 1, 3, 5 and 19 as being obvious over Charak et al. combined with Zav'Yalov et al.; claim 4 as being obvious over Charak et al. and Zav'Yalov et al. combined with Isoai et al.; claims 1, 3, 5, and 19 as being obvious over Charak et al. combined with WO 94/01457 or Ruegg et al.; claim 4 as being obvious over Charak et al. combined with WO 94/01457 or Ruegg et al. and Isoai et al.; and claim 1 as being obvious over Charak et al. combined with WO 94/10313.

Charak et al. is relied on for teaching a composition of immunosuppressants and interferon that is used to generate an anti-cancer effect. Charak et al. is asserted to differ from the present invention in the use of INF α, β, ω, and τ. Cruse is

generally relied on for teaching various interferons and that interferons have immunomodulatory functions.

The present invention is drawn to a composition of immunosuppressants, cyclosporins, FK506, or rapamycin and at least one bioactive peptide comprising the high-affinity binding/anti-lymphoproliferative site of interferons α, β, ω, τ, or recombinant proteins carrying one or more of the sequences comprising the structures of said bioactive peptides for the aim of amplification of immunosuppressants' activities to decrease their therapeutic dose, and as the consequence to avoid their undesirable side effects during organ and tissue transplantation.

The present application requires the presence of the high-affinity binding/anti-lymphoproliferative site of interferons α, β, ω, τ. There is no disclosure in Charak et al. a composition specifically having the high-affinity binding/anti-lymphoproliferative site of interferons α, β, ω, τ. Nor is there any motivation from Charak et al. or Cruse et al. to modify Charak et al. to use the high-affinity binding/anti-lymphoproliferative site of interferons α, β, ω, τ in a composition with immunosuppressants, cyclosporins, FK506, or rapamycin. The compositions of the invention possess the property of increasing the

efficacy of immunosuppresant drugs used during organ and tissue transplantation. There is no disclosure or suggestion in either Charak et al. or Cruse et al. of creating a composition with the specific property of increasing the efficacy of immunosuppresant drugs using during organ and tissue transplantation. As such, there is no motivation in either reference to modify the compositions of Charak et al., which are used in treating cancer, to replace the interferon of Charak et al. specifically the high-affinity binding/anti-lymphoproliferative site of interferons α, β, ω, τ. As such, the present invention is not prima facie obvious over Charak et al. combined with Cruse et al.

The present invention further possesses unexpected properties, which are not suggested by the references. One skilled in the art would find the activity of the present compositions in transplant patients to be unexpected because it has been observed that a monoclonal antibody directed against the extracellular domain of the human INF-α receptor, which inhibits both the binding and biological activity of all type I IFNs tested, exerts a dose-dependent inhibition of a mixed lymphocyte reaction and induces permanent survival of skin allografts in MHC-divergent Cynomologus monkeys treated with a subeffective dose of cyclosporin A. See Tovey et al.

1996, J. Leukocyte Biol. 59 512-517. Tovey et al. was made of record with the IDS of February 28, 2000.

Thus, it is highly unexpected that the type I IFN sequences (the high-affinity binding/anti-lymphoproliferative site of interferons α, β, ω, τ) used in compositions of the invention would amplify immunosuppressant activity in the treatment of transplantation patients. As such, the present invention is not obvious over Charak et al. and Cruse et al.

In addition, the additional references of Zav'Yalov et al.; Isoai et al.; WO 94/01457; Ruegg et al; and WO 94/10313 fail to provide motivation to modify Charak et al. to specifically use the high-affinity binding/anti-lymphoproliferative site of interferons α, β, ω, τ. Nor is there any suggestion in these additional references of the unexpected properties associated with the present invention. As such, the present invention is not obvious over the combined references and withdrawal of the rejections is respectfully requested.

A marked-up version of the amended claim 1 showing all changes is attached hereto.

Pursuant to 37 C.F.R. §§ 1.17 and 1.136(a), Applicants respectfully petition for a one (1) month extension of time for

filing a reply in connection with the present application, and the required fee of $55.00 is attached hereto.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17; particularly, extension of time fees.

Respectfully submitted,

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Marked-up Version Showing Changes

IN THE CLAIMS

Claim 1 has been amended as folllows.

1. (Four Times Amended) A composition comprising immunosuppressants, cyclosporins, FK506, or rapamycin and at least one bioactive peptide ~~corresponding to~~ **comprising** the high-affinity binding/anti-lymphoproliferative site of interferons α, β, ω, τ, or recombinant proteins carrying one or more of the sequences ~~corresponding to~~ **comprising** the structures of said bioactive peptides for the aim of amplification of immunosuppressants' activities to decrease their therapeutic dose, and as the consequence to avoid their undesirable side effects during organ and tissue transplantation ~~or during treatment diseases wherein cyclosporins, FK506 or rapamycin can be exploited~~.